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ORIGINAL ARTICLE

# Early-onset inguinal hernia as risk factor for schizophrenia or related psychosis: a nationwide register-based cohort study

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## Abstract

**OBJECTIVES:** In an earlier interview study, we found that more men with familial schizophrenia had undergone inguinal hernia operation, than men with sporadic schizophrenia. However, there are no other studies published specifically on inguinal hernia and schizophrenia. Therefore, the aim of this study was to carry out a Swedish register-based cohort study on the association between inguinal hernia and schizophrenia or related psychosis.
**METHODS:** Data from the Total Population- and Medical Birth-Registers were used to create a cohort of all individuals born in Sweden 1987–1999 (n=1 406 168). The cohort individuals were linked with the In- and Out-patient Registers and followed from birth to 2015 to identify onset of schizophrenia, schizoaffective disorder and inguinal hernia. Cox proportional hazards regression models were used to assess the association between inguinal hernia before age 13 and risk of developing schizophrenia or schizoaffective disorder during a follow-up from age 13.
**RESULTS:** Inguinal hernia before age 13 was identified in 21 095 individuals, and during the follow-up in total 1314 individuals developed schizophrenia or schizoaffective disorder. The risk of schizophrenia or schizoaffective disorder was higher among individuals with inguinal hernia before age 13, than among individuals without such a diagnosis, especially among the men [adjusted hazard ratio (95% confidence interval); all: 1.44 (1.01–2.06), $p$=0.0452, men: 1.46 (1.01–2.12), $p$=0.0460, women: 0.56 (0.14–2.27), $p$=0.4173].
**CONCLUSIONS:** This study shows that early-onset inguinal hernia is associated with increased risk of developing schizophrenia or schizoaffective disorder, especially in men. Such an association may point to a common biological basis for the development of inguinal hernia and schizophrenia or related psychosis.

## INTRODUCTION

Schizophrenia is a chronic psychotic disorder that affects approximately 0.5% of the population worldwide (Freedman 2003; McGrath *et al.* 2008). It usually afflicts people in late adolescence or early adulthood and continues throughout life (Freedman 2003). The aetiology of schizophrenia is still, in the main, unknown. Nevertheless there is strong evidence for a role of genetic factors in its aetiology (Craddock *et al.* 2005). There are also indications that schizophrenia is a systemic disorder and not only a brain disease (Flyckt 2001; Kirkpatrick *et al.* 2014). A comprehensive review of the literature on comorbid somatic diseases in schizophrenia shows that patients with schizophrenia have higher prevalences of HIV infection and hepatitis, osteoporosis, altered pain sensitivity, sexual dysfunction, obstetric complications, cardiovascular disease (CVD), dental problems and polydipsia than the general population, whereas rheumatoid arthritis and cancer occur less frequently (Leucht *et al.* 2007). Patients with schizophrenia have also an increased mortality compared to the general population (Brown 1997), and approximately half of this excess mortality is rooted in somatic diseases (Munk Laursen *et al.* 2011), of which CVD is the leading cause (Hennekens *et al.* 2005). The metabolic syndrome, a constellation of major risk factors for CVD including insulin resistance, dyslipidemia, diabetes mellitus, hypertension and overweight, is too more common among schizophrenia patients (Allison *et al.* 1999; Dixon *et al.* 1999; Leucht *et al.* 2007; Mukherjee *et al.* 1996; Ryan *et al.* 2003; Saari *et al.* 2005; Wu *et al.* 2013). Furthermore, neurologic abnormalities (i.e. structural and functional brain abnormalities with or without associated minor physical anomalies of the head, eyes, ears, mouth, hands and feet, movement disorders including dyskinesias, parkinsonism and catatonia, sensory abnormalities, neurologic soft signs and epilepsy) may co-exist with schizophrenia (Nasrallah 2005). Also a number of other specific somatic diseases and syndromes, such as autoimmune diseases, head injury, Kallman syndrome and the velocardiofacial syndrome are associated with increased risk of schizophrenia (Benros *et al.* 2011; Karayiorgou *et al.* 1995; Orlovska *et al.* 2014; Vagenakis *et al.* 2004; Verhoeven *et al.* 2013). The somatic abnormality, disease or syndrome either exists before the first diagnosis of schizophrenia (Benros *et al.* 2011; Karayiorgou *et al.* 1995; Nasrallah 2005; Orlovska *et al.* 2014; Sørensen *et al.* 2015; Vagenakis *et al.* 2004; Verhoeven *et al.* 2013) or is acquired during the lifetime after the schizophrenia has been diagnosed, where the schizophrenia illness itself, the lifestyle and the long-term treatment with antipsychotics all may be contributive factors to the development of the somatic comorbidity (Brown *et al.* 1999; Melkersson 2009; Melkersson & Dahl 2004; Nasrallah 2005; Saari *et al.* 2005; Sørensen *et al.* 2013).

In an earlier study, in which 95 patients with schizophrenia were interviewed regarding occurrence of somatic diseases, we found that three (6%) of 48 men with schizophrenia had undergone inguinal hernia operation before 29 years of age (Melkersson 2009). This finding is to be compared with 0.1% occurrence of inguinal hernia in the Swedish male general population in the same age-interval according to Statistics Sweden (www.scb.se, August 2015). All three men reported in addition heredity for schizophrenia (Melkersson 2009). Moreover, in a Danish register-based study (Sørensen *et al.* 2015), the diagnostic group of the digestive system was associated with schizophrenia, and within this group, inguinal hernia was one of the three most common diagnoses.

In Sweden, we have population- and health-registers with satisfactory validity of diagnoses and high technical quality (Dalman *et al.* 2002; Kristjansson *et al.* 1987), which are well suited for epidemiological studies. A recently published review over the last 30 years of Swedish register studies regarding causes for schizophrenia shows that these registers have contributed considerably to our understanding of several risk factors for schizophrenia (Harper *et al.* 2015). In our search in the Medline database, we have however not found any published register studies specifically concerning inguinal hernia or other abdominal wall hernias (Zöller *et al.* 2013) and schizophrenia. Therefore, to verify our finding from the earlier interview study (Melkersson 2009) in an independent and larger context, we carried out a Swedish population-based register study on the occurrence of schizophrenia or related psychosis in individuals with or without inguinal hernia or other abdominal wall hernias.

## MATERIAL & METHODS

The study was approved by the Regional Ethical Review Board, Stockholm, Sweden. A flow diagram of the study population is shown in Figure 1. Data from the Total Population- and Medical Birth-Registers were used to create a cohort of all individuals born in Sweden from January 1, 1987 to December 31, 1999 (n=1 406 168). Individuals who were lacking information about their mothers (n=3 685), had incomplete migration data (n=2 944), were part of multiple births (n=37 375), or had emigrated (n=51 296) or died (n=8 259) before 13 years of age were excluded. The final study cohort consisted of total 1 302 599 individuals living in Sweden at age 13 (Figure 1). Each individual in the study was identified by their personal identity number, which individual information is kept in Swedish registers and that also ensures accurate linkage of information between registers (Ludvigsson *et al.* 2009). However, to protect the integrity of the participating individuals of the study, the two holders of the registers, Statistics Sweden and the National Board of Health and Welfare in Sweden, replaced according to established practice

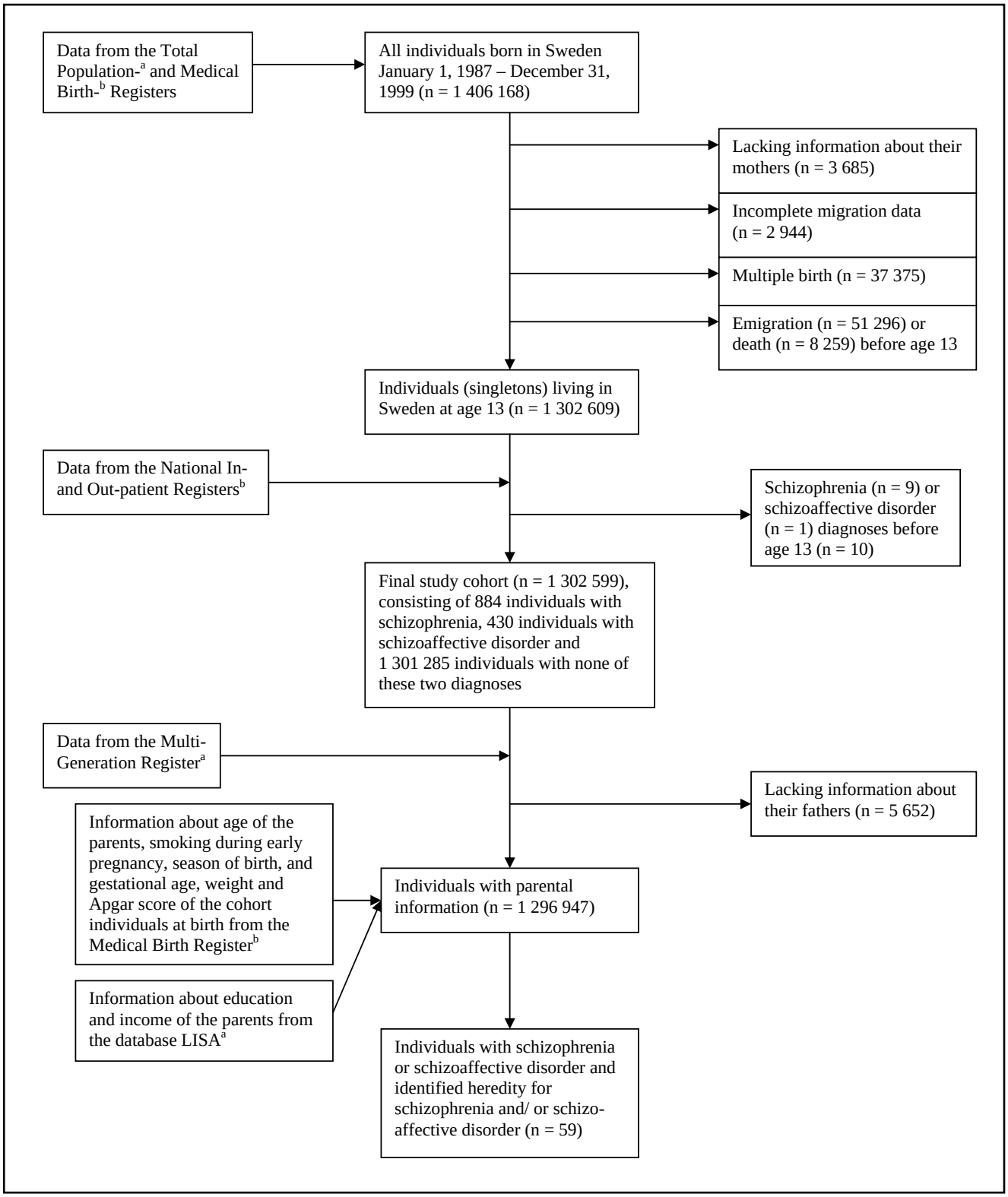



**Fig. 1.** Flow diagram of the study population. [a]Held by Statistics Sweden; [b]Held by the National Board of Health and Welfare in Sweden.

the personal identity numbers by unique serial numbers before delivering the data to us researchers (Ludvigsson *et al.* 2009).

The individuals of the study cohort were linked with the National In- and Out-patient Registers and followed to identify onset of schizophrenia, schizoaffective disorder, inguinal hernia and other abdominal wall hernias including surgery (Zöller *et al.* 2013), and as control, also onset of retained testicle including surgery, from birth until death, emigration or December 31, 2015, whichever came first (Figure 1). The Inpatient Register covers satisfactorily all general and mental hospital

care in Sweden since 1969, and the Outpatient Register all general and mental outpatient care in Sweden since 2001. All diagnoses in the registers are defined according to The International Classification of Diseases (ICD) and all operations according to The Classification of Surgical Procedures (http://www.socialstyrelsen.se). The classification codes used for each diagnosis and operation in this study are given in Table 1. Individuals were categorized from the date of their first contact to a hospital or polyclinic with such a diagnosis and/or operation. In addition, heredity for schizophrenia or schizoaffective disorder was established by linking data on the biological parents of the cohort individuals, derived from the Multi-Generation Register, with the In- and Out-patient Registers (Figure 1). Moreover, information about age of the parents, smoking during early pregnancy, season of birth, and gestational age, weight and Apgar score of the cohort individuals at birth was derived from the Medical Birth Register, while information about education and income of the parents was derived from the database LISA (Figure 1).

To assess the associations between inguinal hernia, other abdominal wall hernias or retained testicle before age 13 and risk of schizophrenia or schizoaffective disorder, we applied Cox proportional hazard (PH) models, using age as timescale. Follow-up started at age 13, and individuals with schizophrenia or schizoaffective disorder before age 13 were excluded (n=10). Individuals were censored at emigration, death or end of follow-up (December 31, 2015). We used a robust sandwich covariance matrix estimate to account for the lack of independence of individuals within the same family. The assumption of PH was visually checked by plotting the Schoenfeld residuals against rank time and fitting a smooth curve with 95% confidence bands. To illustrate the association between inguinal hernia and risk of schizophrenia or schizoaffective disorder, we also calculated and plotted Kaplan-Meier estimates of the cumulative risk to the first occurrence of an event of schizophrenia or schizoaffective disorder. The results are reported both as unadjusted and adjusted hazard ratios (HRs) with 95% confidence interval (CI) and as incidence rates (IRs) per 100 000 person-years at risk with exact 95% CI.

Potential confounders were selected for adjustment based on directed acyclic graphs (Greenland *et al.* 1999) taking into account prior knowledge regarding their associations with inguinal hernia, schizophrenia and schizoaffective disorder (Bertelsen & Gottesman 1995; Christianson 1980; Craddock *et al.* 2005; Czeizel 1980; Harper *et al.* 1975, 2015; Kelsey *et al.* 1978; Kumar *et al.* 2002; Melkersson 2009; Mortensen *et al.* 1999; Nannestad Jorgensen *et al.* 1998; Peevy *et al.* 1986; Unal *et al.* 2016; Zammit *et al.* 2009). Hence, we adjusted for heredity for schizophrenia and/or schizoaffective disorder, father's age at time of birth of the cohort individual, smoking during early pregnancy, season of birth, gestational age, and birth weight in relation to gestational age. Furthermore, to adjust for unmeasured and measured environmental and genetic confounding factors shared by siblings, we estimated a stratified Cox PH model conditional on sibling cluster (D'Onofrio *et al.* 2013). Only clusters with at least one schizophrenia- or schizoaffective disorder-event individual and at

**Tab. 1.** Classification codes used for each diagnosis and operation in the study

| Diagnosis and operation | ICD-8 codes[a] in 1969-1986 | ICD-9 codes[a] in 1987-1996 | ICD-10 codes[a] in 1997-2015 | Operation codes[b] in 1969-1996 | Operation codes[b] in 1997-2015 |
|---|---|---|---|---|---|
| Schizophrenia | 295.00–295.30, 295.60, 295.99 | 295A–295D, 295G, 295W, 295X | F20.0–F20.3, F20.5, F20.6, F20.9 | | |
| Schizoaffective disorder | 295.70 | 295H | F25.0–F25.2, F25.8, F25.9 | | |
| Inguinal hernia Surgery | 550.99, 552.99 | 550A, 550B, 550X | K40.0–K40.4, K40.9 | 4200–4206 | JAB |
| Femoral hernia[c] Surgery | 551.00, 553.00 | 551A, 552A, 553A | K41.0–K41.4, K41.9 | 4210, 4211, 4213 | JAC |
| Epigastric hernia[c] Surgery | 551.20, 553.20 | 551C, 552C, 553C | K43.6, K43.7, K43.9 | 4250, 4251 | JAE |
| Incisional hernia[c] Surgery | 551.21, 553.21 | | K43.0–K43.2 | 4240–4244 | JAD |
| Umbilical hernia[c] Surgery | 551.10, 553.10 | 551B, 552B, 553B | K42.0, K42.1, K42.9 | 4260–4263 | JAF |
| Retained testicle Surgery | 752.10 | 752F | Q53.0–Q53.2, Q53.9 | 6790 | KFH00 |

[a]According to The International Classification of Diseases (ICD), 8th, 9th, 10th revisions (http://www.socialstyrelsen.se)
[b]According to The Classification of Surgical Procedures (http://www.socialstyrelsen.se)
[c]Belongs to the group of other abdominal wall hernias (Zöller *et al.* 2013)

least one event-free individual at the age of event in the schizophrenia or schizoaffective disorder individual, contribute to the estimations in the sibling analyses; informative sample size is thus reported for sibling analyses. We also performed subgroup analyses by sex and heredity for schizophrenia and/ or schizoaffective disorder. Finally, as a control, we explored the association between retained testicle before age 13 and risk of schizophrenia or schizoaffective disorder.

A *p*-value of less than 0.05 was considered statistically significant. All calculations were made with the statistical program SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

## RESULTS

The study population included 1 302 599 individuals (48.7% females) and the length of follow-up was maximally 16.9 (median 9) years from their 13th birthday. Characteristics of the study cohort are described in Table 2. During the follow-up (12 675 906 person-years), 1 314 individuals developed schizophrenia or schizoaffective disorder (Figure 1). The mean age (standard deviation) at diagnosis of schizophrenia or schizoaffective disorder was 21.5 (3.0) years.

The IRs with 95% CI of schizophrenia or schizoaffective disorder among individuals with a diagnosis of inguinal hernia, other abdominal wall hernias or retained testicle before age 13 are shown in Table 3 and the HRs with 95% CI are given in Figure 3. The risk of schizophrenia or schizoaffective disorder was significantly higher among individuals with a diagnosis of inguinal hernia before age 13, than among individuals without [Figures 2A and 3; adjusted hazard ratio (95% CI): 1.44 (1.01–2.06), $p$=0.0452]. This association was seen especially in the men, and remained significant in the sibling analysis of men (Figures 2B and 3). In contrast, among individuals with or without a diagnosis of

**Tab. 2.** Characteristics of the study cohort.

| Characteristic | No diagnosis of inguinal hernia before age 13 | A diagnosis of inguinal hernia before age 13 |
|---|---|---|
| All (n) | 1 281 504 | 21 095 |
| Sex[a] | | |
| men | 651 329 (50.8) | 17 193 (81.5) |
| women | 630 175 (49.2) | 3 902 (18.5) |
| Highest level of education achieved by either parent[a] | | |
| > 9 years | 1 149 933 (89.7) | 18 894 (89.6) |
| 9 years | 103 701 (8.1) | 1 731 (8.2) |
| < 9 years | 16 571 (1.3) | 276 (1.3) |
| missing | 11 299 (0.9) | 194 (0.9) |
| Household income categorized into fifths at time of birth of the cohort individual[a] | | |
| 1 (lowest) | 243 803 (19.0) | 4 053 (19.2) |
| 2 | 258 563 (20.2) | 4 253 (20.2) |
| 3 | 260 067 (20.3) | 4 265 (20.2) |
| 4 | 259 276 (20.2) | 4 299 (20.4) |
| 5 (highest) | 254 572 (19.9) | 4 138 (19.6) |
| missing | 5 223 (0.4) | 87 (0.4) |
| Parent born outside Sweden[a] | | |
| father | 147 872 (11.5) | 2 235 (10.6) |
| mother | 133 642 (10.4) | 1 966 (9.3) |
| missing | 5 679 (0.4) | 89 (0.4) |
| Mother living with the father at time of birth of the cohort individual[a] | | |
| yes | 1 111 179 (86.7) | 18 073 (85.7) |
| no | 61 322 (4.8) | 1 101 (5.2) |
| missing | 109 003 (8.5) | 1 921 (9.1) |
| Mother's age at time of birth of the cohort individual (year)[b] | 29.0 (5.1) | 28.9 (5.2) |
| Father's age at time of birth of the cohort individual (year)[b] | 31.9 (6.1) | 31.8 (6.1) |
| missing (n) | 5 563 | 89 |
| Smoking during early pregnancy[a] | | |
| non–smoker | 937 771 (73.2) | 14 128 (67.0) |
| 1–9 cigarettes/ day | 156 647 (12.2) | 3 114 (14.8) |
| > 9 cigarettes/ day | 91 969 (7.2) | 2 016 (9.6) |
| missing | 95 117 (7.4) | 1 837 (8.7) |
| Season of birth[a] | | |
| January – March | 333 433 (26.0) | 5 739 (27.2) |
| April – December | 948 071 (74.0) | 15 356 (72.8) |
| Gestational age[a] | | |
| < 38 weeks | 120 745 (9.4) | 4 625 (21.9) |
| 38–40 weeks | 821 505 (64.1) | 12 198 (57.8) |
| > 40 weeks | 316 322 (24.7) | 3 825 (18.1) |
| missing | 22 932 (1.8) | 447 (2.1) |
| Birth weight (g)[b] | 3 550.3 (547.8) | 3 291.0 (783.9) |
| < 3000 g[a] | 164 402 (12.8) | 5 522 (26.2) |
| 3000–3999 g[a] | 849 376 (66.3) | 11 999 (56.9) |
| ≥ 4000 g[a] | 243 944 (19.0) | 3 100 (14.7) |
| missing[a] | 23 782 (1.9) | 474 (2.2) |
| Birth weight in relation to gestational age[a] | | |
| small for age | 30 317 (2.4) | 1 494 (7.1) |
| normal | 1 182 196 (92.3) | 18 519 (87.8) |
| large for age | 43 434 (3.4) | 556 (2.6) |
| missing | 25 557 (2.0) | 526 (2.5) |
| Apgar score at 1 min[a] | | |
| 0–6 | 49 490 (3.9) | 1 354 (6.4) |
| 7–10 | 1 201 174 (93.7) | 19 112 (90.6) |
| missing | 30 840 (2.4) | 629 (3.0) |

Abbreviations: g = gram, min = minute, n = number, SD = standard deviation; [a]Data are given as n (%), [b]Data are given as mean (SD)

other abdominal wall hernias or retained testicle before age 13, the risk of schizophrenia or schizoaffective disorder did not differ (Figure 3).

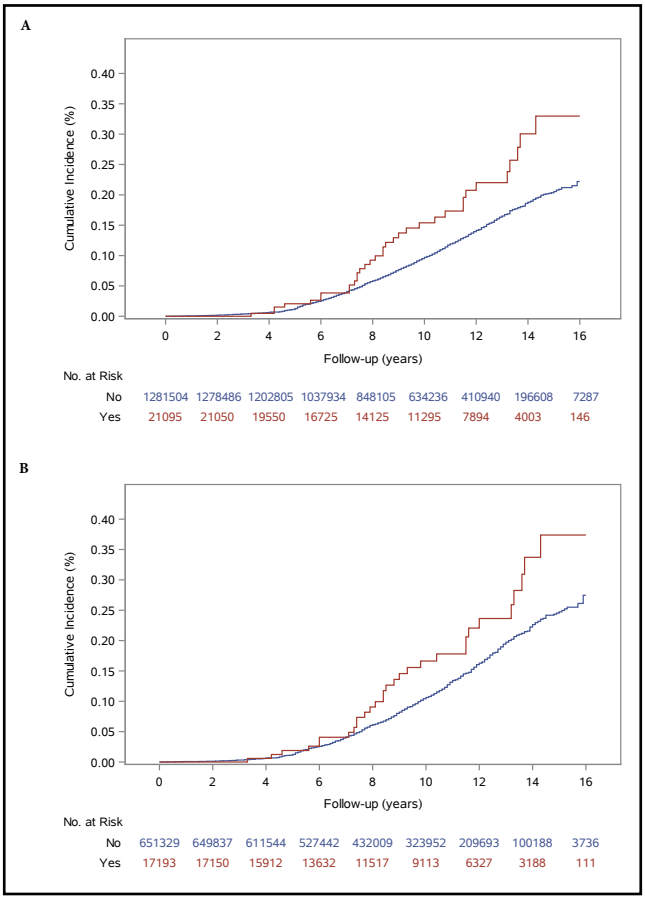



**Fig. 2.** Kaplan-Meier estimate of cumulative incidence of schizophrenia or schizoaffective disorder in percentage (%) in relation to follow-up time in years among all individuals (A), or among only male individuals (B), with (red line) or without (blue line) a diagnosis of inguinal hernia before age 13. Follow-up of the individuals started at 13 years of age and the number of individuals at risk with or without inguinal hernia (in red or blue) at different follow-up points of time are given below the figures.

However, regarding the subgroup analysis by heredity for schizophrenia and/ or schizoaffective disorder, the number of individuals with heredity for schizophrenia and/ or schizoaffective disorder and a diagnosis of inguinal hernia before age 13 was in this study too small to achieve enough statistical power for disclosing or dismissing with certainty an association (Table 4).

In the original study population 37 375 individuals who were part of multiple births were included (Figure 1), of whom 35 290 were living in Sweden at age 13. A separate investigation of these individuals, of whom none was diagnosed with schizophrenia or schizoaffective disorder before age 13, showed that they more often had a diagnosis of inguinal hernia before age 13, than the singletons [1 308/35 290 (3.71%) vs 21 095/1 302 599 (1.62%)]. During the follow-up, 25 individuals who were part of multiple births developed schizophrenia or schizoaffective disorder. However, none (0%) of these 25 individuals had a diagnosis of inguinal hernia before age 13.

The small group of individuals who developed schizophrenia or schizoaffective disorder before age 13 included 10 individuals (five females) with no identified heredity for schizophrenia and/ or schizoaffective disorder (Figure 1). A separate investigation of the occurrence of inguinal hernia, other abdominal wall hernias or retained testicle before age 13 only among these 10 individuals, showed that one individual (10%) had a diagnosis of inguinal hernia, whereas none (0%) had diagnoses of other abdominal wall hernias or retained testicle.

## DISCUSSION

In this register-based cohort study, we found that early-onset inguinal hernia diagnosed before age 13 is associated with an increased risk of developing schizophrenia or schizoaffective disorder, especially in men. The result remained when controlling for possible confounders as well as in an additional sibling cohort-analysis match-

**Tab. 3.** Incidence rates of schizophrenia or schizoaffective disorder associated with a diagnosis of inguinal hernia, other abdominal hernias or retained testicle before age 13.

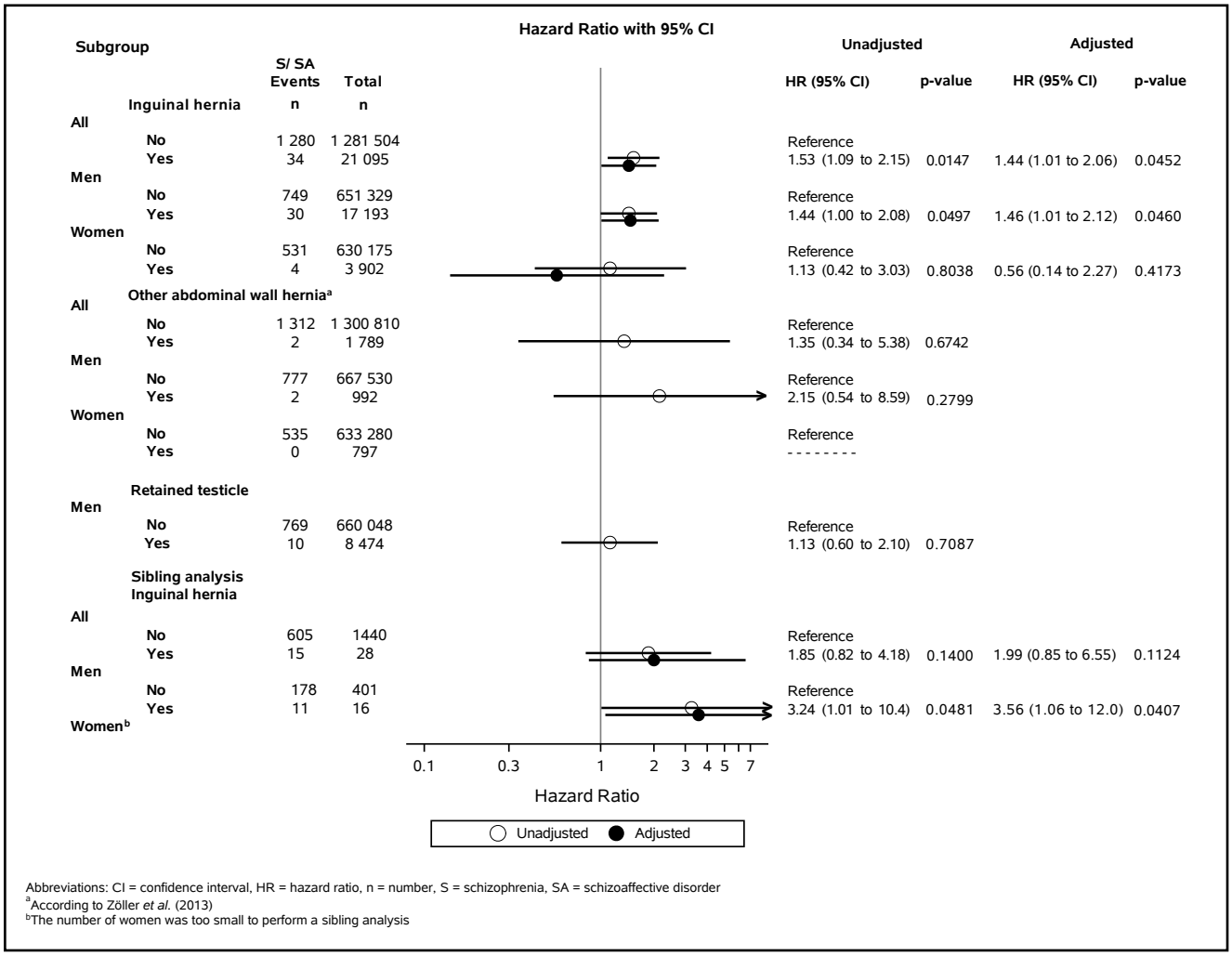
| Somatic disease | Schizophrenia or schizoaffective disorder | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | All | | | Men | | | Women | | |
| | Cases (n) | FU time[a] | IR (95 % CI)[b] | Cases (n) | FU time[a] | IR (95 % CI)[b] | Cases (n) | FU time[a] | IR (95 % CI)[b] |
| Inguinal hernia | 34 | 4.84 | 7.02 (4.86–9.81) | 30 | 3.94 | 7.61 (5.14–10.87) | 4 | 0.90 | 4.43 (1.21–11.35) |
| No inguinal hernia | 1280 | 291.26 | 4.39 (4.16–4.64) | 749 | 148.11 | 5.06 (4.70–5.43) | 531 | 143.15 | 3.71 (3.40–4.04) |
| Other abdominal hernias[c] | 2 | 0.39 | 5.14 (0.62–18.58) | 2 | 0.22 | 9.31 (1.13–33.62) | 0 | 0.17 | 0.00 (na–21.21) |
| No other abdominal hernias[c] | 1312 | 295.71 | 4.44 (4.20–4.68) | 777 | 151.83 | 5.12 (4.76–5.49) | 535 | 143.88 | 3.72 (3.41–4.05) |
| Retained testicle | na | na | na | 10 | 1.88 | 5.32 (2.55–9.78) | na | na | na |
| No retained testicle | na | na | na | 769 | 150.16 | 5.12 (4.77–5.50) | na | na | na |

Abbreviations: CI = confidence interval, FU = follow-up, IR = incidence rate, n = number, na = not applicable
[a]Expressed as 100 000 person-years at risk; [b]Number of new cases per 100 000 person-years at risk; [c]According to Zöller *et al.* (2013)

**Tab. 4.** Risk of schizophrenia or schizoaffective disorder associated with a diagnosis of inguinal hernia before age 13 in individuals with or without heredity for schizophrenia and/ or schizoaffective disorder.

| Variable | | Schizophrenia or schizoaffective disorder | | |
|---|---|---|---|---|
| | | Cases (n) | IR (95% CI)[a] | HR (95% CI) |
| Heredity for schizophrenia and/ or schizoaffective disorder | Inguinal hernia | 2 | 66.71 (8.08–240.99) | 2.06 (0.50–8.51) |
| | No inguinal hernia | 57 | 32.68 (24.75–42.34) | reference 1.00 |
| No heredity for schizophrenia and/ or schizoaffective disorder | Inguinal hernia | 31 | 6.47 (4.40–9.18) | 1.47 (1.03–2.10) |
| | No inguinal hernia | 1213 | 4.21 (3.97–4.45) | reference 1.00 |

Abbreviations: CI = confidence interval, HR = hazard ratio, IR = incidence rate, n = number
[a]Number of new cases per 100 000 person-years at risk




Abbreviations: CI = confidence interval, HR = hazard ratio, n = number, S = schizophrenia, SA = schizoaffective disorder
[a]According to Zöller *et al.* (2013)
[b]The number of women was too small to perform a sibling analysis

**Fig. 3.** Hazard ratios of schizophrenia or schizoaffective disorder among individuals with a diagnosis of inguinal hernia, other abdominal wall hernias or retained testicle before age 13, and among siblings to individuals with a diagnosis of inguinal hernia before age 13. Solid vertical line crossing at 1.0 is the reference including all individuals or all siblings with no diagnosis of the somatic disease in question.

ing for shared genetic and environmental risks. Neither did a diagnosis before age 13 of retained testicle, which is caused by factors other than those for inguinal hernia (Foresta *et al.* 2008; Franz 2008; Kojima *et al.* 2009; Lynen Jansen *et al.* 2004) and was used as control, increase the risk of developing schizophrenia or schizoaffective disorder.

This association between inguinal hernia and schizophrenia or schizoaffective disorder is of great interest, as it is known that altered collagen synthesis- and degradation routes underlie development of inguinal hernia in young men (Bellón *et al.* 2001; Franz 2008; Friedman *et al.* 1993; Lynen Jansen *et al.* 2004; Szczesny *et al.* 2006); at the same time as the three most signifi-

cantly upregulated mRNA transcripts in post-mortem brains of individuals with schizophrenia or schizoaffective disorder compared with matched controls derive from the genes heat shock protein family A member 6 (*HSPA6*), serpin family H member 1 (*SERPINH1*) and BCL2 associated athanogene 3 (*BAG3*), which all code proteins involved in the collagen metabolism in the human brain and body (Fillman *et al.* 2013). Interestingly, our finding is further supported by the fact that two genetic syndromes; Marfan syndrome, an autosomally dominantly inherited connective tissue defect disorder related to recurrent inguinal hernia, also may be presenting with schizophrenia-like psychosis (Dietz & Pyeritz 1995; Lindeboom & Westerveld-Brandon 1950; Van Den Bossche *et al.* 2012) and the velocardiofacial syndrome, besides its typical features, also may include other anomalies such as inguinal hernia and schizophrenia (Karayiorgou *et al.* 1995; Matsuoka *et al.* 1998).

To the best of our knowledge, this is the first register-based study published, showing an association between early-onset inguinal hernia and development of schizophrenia or schizoaffective disorder. The question is what the common biological basis for inguinal hernia and schizophrenia or related psychosis is. However, this is still not known. Nevertheless, it is interesting that a biological mechanism proposed for inguinal hernia formation is abnormal collagen metabolism and that the fibroblast is the major source for collagen synthesis and turnover, and therefore defects in fibroblast function are an important mechanism for subsequent tissue collagen disease (Franz 2008; Lynen Jansen *et al.* 2004). Furthermore, in fibroblasts from schizophrenia patients, the transport of the amino acid tyrosine across cell membranes is aberrant (Flyckt *et al.* 2001; Hagenfeldt *et al.* 1987; Ramchand *et al.* 1996), at the same time as tyrosine is the precursor to dopamine formation in brain and body; and the dopamine hypothesis, postulating a dysregulation of dopamine transmission in the brain, remains the main theory for the pathophysiology of schizophrenia (Carlsson 1978; Seeman & Seeman 2014).

Multiple birth has been reported in several previous studies to be associated with increased risk of early-onset inguinal hernia (Bakwin 1971; Chung & Myrianthopoulos 1975; Czeizel 1980; Sawaguchi *et al.* 1975), and also in this study, a diagnosis of inguinal hernia before age 13 was more common in individuals who were part of multiple births than in singletons. As causative factors for inguinal hernia in multiple birth can be assumed to, at least in part, differ from those for inguinal hernia in general (Bakwin 1971; Sawaguchi *et al.* 1975), we chose to exclude all individuals who were part of multiple births from our final study cohort.

Childhood-onset schizophrenia (defined by an onset of schizophrenia before age 13) is a rare early-onset variant of the more common adult-onset schizophrenia (Asarnow & Forsyth 2013; Kolvin 1971; Lachman 2014; Nicolson & Rapoport 1999). Although the current diagnostic classification systems DSM-5 (American Psychiatric Association 2013) and ICD-10 (http://www.socialstyrelsen.se) use the same criteria to diagnose schizophrenia in children as in adults (Lachman 2014), childhood-onset schizophrenia is associated with a greater familial aggregation of schizophrenia spectrum disorders and a higher rate of rare allelic variants than the adult-onset schizophrenia (Asarnow & Forsyth 2013). In this study, we therefore focused on the individuals with adult-onset schizophrenia or schizoaffective disorder and excluded the 10 individuals with onset of these two disorders before 13 years of age from the final study cohort. However, when we separately investigated the occurrence of inguinal hernia before age 13 only in these 10 individuals, we found that 1 (10%) of the individuals had inguinal hernia, possibly pointing to that the rate of early-onset inguinal hernia even is higher in the childhood-onset schizophrenia or schizoaffective disorder group, than in the adult-onset group.

The major strength of this study includes its prospective and population-based design, ensuring that all events of schizophrenia or schizoaffective disorder were recorded prospectively and independently of the exposures (the somatic diseases in question) and therefore not subject to selection or recall bias. A further strength also includes the narrow diagnostic selection of only schizophrenia and its related schizoaffective disorder, and not of all nonaffective psychoses, allowing investigation of specific associations between inguinal hernia, other abdominal wall hernias or retained testicle, and schizophrenia or related psychosis. The limitations, on the other hand, consist of lack of analyses of associations between the somatic diseases in question and schizophrenia or schizoaffective disorder with onset between 29–40 years of age or late-onset, i.e. after the age of 40 (Harris & Jeste 1988; Howard *et al.* 2000), which could not be carried out in this study that only allowed a follow-up of the cohort individuals up to maximally age 28. With regard to inguinal hernia also occuring more often in men than in women (Lau *et al.* 2007), the finding in this study of a gender difference in the association between inguinal hernia and schizophrenia or schizoaffective disorder was not unexpected. However, it cannot be ruled out that also the as-a-rule later onset of schizophrenia or schizoaffective disorder in women than in men (DeLisi 1992; Häfner 2003), could have contributed to the lack of association in the women. The limitations also include lack of data on the variables heredity for inguinal hernia, low maternal weight gain during pregnancy, and alcohol and/ or substance use during pregnancy, which are possible risk factors for both inguinal hernia and schizophrenia or related psychosis (Chung & Myrianthopoulos 1975; Lau *et al.* 2007; Liem *et al.* 1997; Mackay *et al.* 2017; Perlmutter 1974; Popova *et al.* 2016; Zammit *et al.* 2009). However, as the sibling cohort-analysis showed a similar result to the cohort-analysis itself in this study, it is unlikely that these variables can explain the observed associations.

In conclusion, this study shows that early-onset inguinal hernia diagnosed before age 13 is associated with an increased risk of developing schizophrenia or schizoaffective disorder, especially in men. Interestingly, this association may point to a common biological basis for the development of inguinal hernia and schizophrenia or related psychosis.

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